RESPONSE TO THIRD OFFICE ACTION

A. Status of the Claims

Claims 2-4 and 67-68 were pending at the time of the action. Claim 68 has been canceled herein without prejudice or disclaimer. Claims 2-4 have been amended to correct antecedent basis. Claim 67 has been amended pursuant to the election to prosecute subject matter relating to maize plants transformed with a fatty acid desaturase gene in this case. Claims 2-4 and 67 are now pending and presented for reconsideration.

B. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Action states that claims 2-4 and 67-68 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. However, only a rejection of claim 68 is set forth in the action. It is therefore believed that only this claim has been rejected.

Claim 68 was rejected for depending upon a canceled claim. In response it is noted that the claim has been canceled herein and thus the rejection is now moot.

C. Rejection of Claims Under 35 U.S.C. §112, First Paragraph – Written Description

The Action rejects the claims under 35 U.S.C. §112, first paragraph, as lacking an adequate written description. In particular, it is asserted that the claims are broadly drawn to fertile transgenic maize plants transformed with a laundry list of genes involved in grain composition, but that the specification does not provide guidance for isolation and identification of these genes. *Eli Lilly* in particular is cited for the proposition that a claimed invention must be defined by a precise definition, such as by structure, formula, etc., and MPEP §2163, p.156 is cited for the principle that a biomolecule cannot be defined merely by function when the function

is not correlated with a structure. It is thus asserted that the sequences were not described such that methods of using the sequences to create transgenic plants were also not described. Applicants respectfully traverse.

Applicants first note that they are claiming maize plants transformed with fatty acid desaturase genes and are not claiming the gene sequences themselves, as these sequences were ***known***. All of the authority cited in the Action relates to the situation in which an applicant is claiming a specific nucleic acid sequence, yet has not described the sequence being claimed. In *Eli Lilly*, for example, the subject patent claimed a novel human insulin-encoding cDNA sequence, not use of a known sequence. A lack of written description was found because the specification failed to describe the sequence that was claimed. *The Regents of The University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). None of the authority relates to the situation where the gene itself is known, but novel compositions have been created using that gene. *Eli Lilly* and the corresponding line of authority cited in the Action are therefore inapposite to the current situation.

It is well settled that the specification need not disclose what is well-known to those skilled in the art and ***preferably omits*** what is well-known and already available to the public. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Further, written description must be reviewed from the perspective of one of skill in the art. *Wang Labs., Inc. v. Toshiba Corp.*, 993 F.2d 858, 863 (Fed. Cir. 1993). There is therefore an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy written description. USPTO Written Description Guidelines, Fed. Reg. Vol. 66, p. 1105. Applicants need not specifically recite what is well known.

Numerous examples of known fatty acid desaturases are found in the literature. Among these, McDonough *et al.* (**Exhibit A**) ("Specificity of unsaturated fatty acid-regulated expression of the Saccharomyces cerevisiae OLE1 gene."; *J Biol Chem.* 1992 Mar 25;267(9):5931-6) describe a *Saccharomyces cerevisiae* OLE1 gene encoding delta-9 fatty acid desaturase, an enzyme which forms the monounsaturated palmitoleic (16:1) and oleic (18:1) fatty acids from palmitoyl (16:0) or stearoyl (18:0) CoA. Fox *et al.* (**Exhibit B**) ("Stearoyl-acyl carrier protein delta 9 desaturase from *Ricinus communis* is a diiron-oxo protein." *Proc Natl Acad Sci U S A.* 1993 Mar 15;90(6):2486-90) describe a gene encoding a stearoyl-acyl carrier protein delta 9 desaturase from castor that was expressed in *Escherichia coli.* The authors compared the primary structures of catalytically diverse proteins to identify conserved amino acid motifs involved in eukaryotic fatty acid desaturation.

Reddy *et al.* (Abstract - **Exhibit C**) ("Isolation of a delta 6-desaturase gene from the cyanobacterium *Synechocystis* sp. strain PCC 6803 by gain-of-function expression in *Anabaena* sp. strain PCC 7120" *Plant Mol Biol.* 1993 May;22(2):293-300) describe the cloning of a delta 6-desaturase from the cyanobacteria *Synechocystis* that is responsible for the conversion of linoleic acid (18:2) to gamma-linolenic acid (18:3 gamma). A delta 12-desaturase gene linked to the delta 6-desaturase gene was also identified and expression of the delta 6- and delta 12-desaturases in *Synechococcus* deficient in both desaturases carried out to result in the production of linoleic acid and gamma-linolenic acid. Arondel *et al.* (Abstract - **Exhibit D**) ("Map-based cloning of a gene controlling omega-3 fatty acid desaturation in *Arabidopsis.*" *Science.* 1992 Nov 20;258(5086):1353-5) describe a gene from *Arabidopsis thaliana* that encodes an omega-3 desaturase. Transgenic tissues of both mutant and wild-type plants of the model dicotyledonous plant *Arabidopsis thaliana* were found to have significantly increased amounts of the fatty acid

produced by this desaturase. PCT Application Publ. No. WO 91/13972 describes plant Δ9 desaturases (**Exhibit E**), European Patent Application Publ. No. EP 0616644 describes soybean and Brassica Δ15 desaturases (**Exhibit F**), and European Patent Application Publ. No. 0537178 describes soybean stearoyl-ACP desaturases (**Exhibit G**).

Finally, the specification itself describes in detail how such fatty acid desaturase genes would be used to alter grain composition traits. For example, it is taught that genes may be introduced to alter the balance of fatty acids present in seed oil providing a more healthful or nutritive feedstuff, and may be used to block expression of enzymes involved in fatty acid biosynthesis to alter proportions of fatty acids present. As explained, changes in oil properties may be achieved by altering the type, level, or lipid arrangement of the fatty acids present in the oil. Among representative catalytic steps mentioned for modification include the desaturations from stearic to oleic acid and oleic to linolenic acid resulting in the respective accumulations of stearic and oleic acids.

These examples demonstrate that genes encoding fatty acid desaturases were well known in the art and that the specification fully describes their use of altering grain composition traits. What was not known in the prior art was that they could be expressed for benefit in maize. The inventors have overcome this deficiency and for the first time describe methods enabling the expression of desaturases to alter maize grain composition traits. No assertion has been made that the transformation of maize generally has not been described and the specification teaches transformation with numerous different genes. As fatty acid desaturase sequences were well known in the art, Applicants need not, and preferably do not, recite these sequences in the specification. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

In view of the foregoing, removal of the rejection is respectfully requested.

D. Rejection of Claims Under 35 U.S.C. §112, First Paragraph - Enablement

The Action rejects claims 2-4 and 67-68 under 35 U.S.C. §112, first paragraph as not being enabled. In particular, it is alleged that genes for altering fatty acid composition were not sufficiently taught and that undue experimentation would be required to express a grain composition trait such as a desaturase due to unpredictability and past failure of others in expressing such genes in plants.

In response, Applicants first note that the current claims are directed to the expression of a fatty acid desaturase in maize. The Action does not contest the fact that the specification fully enables transformation of maize with heterologous genes. Rather, it is alleged that such genes were not disclosed. However, as set forth above, fatty acid desaturase genes were ***well known in the art*** at the time of filing. Applicants have established this with references in the published literature establishing this fact. **Exhibits A-G**. It is well settled that for purposes of satisfying the enablement requirement of §112 an applicant need not disclose and ***preferably omits*** what is well known in the art. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

The information provided therefore establishes enablement for the claimed invention. Routine experimentation is irrelevant to enablement, as the applicable legal standard is undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Examples further need not be presented for every embodiment of an invention as there is no requirement of actual reduction to practice prior to filing. *In re Borkowski*, 164 U.S.P.Q. 624 (CCPA 1970).

With regard to whether a fatty acid desaturase would be expected to alter the phenotype of a maize plant sufficient to distinguish the plant from others, Applicants have attached the Declaration of Dr. Virginia Ursin as **Appendix A**. Applicants initially note that the first paragraph of the Declaration has a typographical error in which it is stated that Monsanto Company is the parent company of wholly owned subsidiaries "Calgene Inc. and Monsanto Company." This should state that Monsanto is the parent company of Calgene Inc. and DEKALB Genetics Corporation.

In the Declaration Dr. Ursin describes studies showing that the expression of Δ6 and Δ15 desaturases in maize results in an alteration in the fatty acid profile of corresponding transgenic plants that renders them identifiable over the corresponding non-transgenic plants. Ursin Declaration, ¶6-7. As explained, the results showed that alteration of fatty acid profiles in maize occurs in a predictable manner that is consistent with the enzymatic activity of the fatty acid desaturase that is introduced. Ursin Declaration, ¶7. This evidence therefore establishes that expression of a fatty acid desaturase in maize would in fact be expected to alter the grain composition in a predictable manner that would distinguish transgenic plants from corresponding non-transgenic plants. Given this evidence and the legal standards presented above, enablement of the full scope of the claims has been demonstrated in full compliance with 35 U.S.C. §112, first paragraph. Removal of the rejection is thus respectfully requested.

E. Rejections Under 35 U.S.C. §103(a)

The Action rejects claims 2-4 and 67 under 35 U.S.C. §103 as being obvious over Tomes *et al.* (U.S. Patent 5,886,244 or 6,258,999) in view of each of Shewmaker *et al.* (U.S. 5,349,123) or Barry *et al.* (5,498,830). In particular, it is asserted that it would have been obvious for one of

skill in the art to introduce a gene conferring a grain composition trait into maize using the method allegedly taught by Tomes *et al.* for transformation of maize.

In response, Applicants initially note that the rejection does not appear to address expression of a fatty acid desaturase gene. The current claims have been focused to cover corn plants transformed with fatty acid desaturase genes, which was also present in the original claims. Should the rejection be maintained, Applicants therefore respectfully request that any subsequent Action be made non-final.

With respect to the rejection made, Applicants note that a reasonable expectation of success in arriving at the claimed invention was completely absent among those of ordinary skill in the art at the time of filing, as evidenced by the failure of others to engineer grain composition traits and past difficulty of others in engineering maize in particular. The past failures of others are expressly documented in the enablement rejection in the Action itself, as well as in the references provided with the Action. For example, the Action states that "[t]he process of altering fatty acid composition in transformed plants is [] unpredictable." Action at p.6, bottom ¶. In support of this, the Action cites Post-Beittenmiller (1989) as teaching that transformation with an acyl carrier protein gene failed to produce any detectable phenotypic change in fatty acid synthesis or accumulation even though acyl carrier protein is involved in fatty acid synthesis or accumulation. The Action also cites Stephanopoulos *et al.* (1993) for the proposition that "plant transformation for the modification of fatty acid accumulation has not been generally successful, that few eukaryotic organisms have had their metabolic pathways successfully altered, and that such alteration of metabolic pathways and accumulated metabolic products is limited by lack of knowledge of the rate limiting steps, and the evolving resistance of metabolic pathways to change even when a single enzyme or single step is altered." Action p.7, top ¶.

The comments in the Action firmly establish that a reasonable expectation of success in arriving at the claimed invention was lacking among those of ordinary skill in the art at the time of filing absent use of the teaching in the specification. The Action itself indicates that expression of genes affecting fatty acid composition in plants was fraught with failures of others and warnings of unpredictability in the art. Applicants' specification may not be used to cure this defect without impermissible hindsight reconstruction. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965). Further, the reasonable expectation of success, as with the other elements of a *prima facie* case of obviousness, must be supported on the record by "substantial evidence," not personal opinion or unsupported conclusion. *See In re Gartside*, 203 F.3d 1305, 1314-15 (Fed. Cir. 2000); 5 U.S.C. § 706(A), (E), 1994; *see also In re Zurko,* 59 USPQ 2d 1693 (Fed. Cir. 2001). Given the unpredictability found by others, this evidence is lacking.

Applicants note that Tomes *et al.* cannot cure the failures of others to provide a reasonable expectation of success because it fails to describe a single actual fertile transgenic maize plant. Tomes is ***entirely prophetic*** with respect to such a plant. The ability to introduce and express any given transgene in maize therefore would have been pure conjecture prior to the studies of Applicants. The expectation of success must be shown in the prior art, not in Applicants' disclosure. It is respectfully submitted that no such showing has been made.

In further support of the non-obviousness of the claims, Applicants have attached a Rule 132 Declaration submitted in a previous case of Assignee's executed by Professor David Somers **(Exhibit H)**, an expert in the area of plant physiology, including corn tissue and cell culture. Dr.

Somers presents articles and reviews published in early to mid-1990s that clearly evidence the long-felt but unresolved need, the failure of others to produce a fertile transgenic corn plant, skepticism relating to the route used by Applicants, and recognition by the art of the significance of the achievement of fertile transgenic corn. In particular, Dr. Somers points to an article in the journal *Science*, published shortly after the announcement that fertile, transgenic corn had been achieved, that begins by noting that the achievement of fertile, transgenic corn is "the capstone of almost a decade's efforts to genetically engineer this country's most important crop," and then continues by noting the "years of frustration and a renewed effort to genetically engineer corn begun by Carol Rhodes and her colleagues." Citing a 1981 *Scientific American* review as evidence of the long-felt need for methods to transform cereals, Dr. Somers concluded that as of early 1990, one of ordinary skill in the art would be aware of at least a decade of failures in achieving fertile, transgenic corn plants.

Further documents also evidence the long felt but unresolved need for the invention and the failure of others to achieve the invention, including scientific accolades of peers in the research community for the ultimate achievement of corn transformation, and evidence of rapid adoption by the art, as further secondary evidence of nonobviousness. Rhodes *et al.* (*Science*, 240, 204 (1988)) **(Exhibit I)**, referred to in the *Science* article discussed above, is particularly relevant. The Rhodes article evidences that while various genes could readily be introduced into corn protoplasts via electroporation, of 38 transformed plants derived from 10 different transformants, none were found to be fertile. *Id.*, p. 206, col. 3. The Rhodes article evidences the failure of others to achieve fertile, transgenic corn, and demonstrates that the technical breakthrough of the present invention involves not the mere introduction of DNA into the corn

genome, but also the ability to do so in a manner that achieves selection of fertile, transgenic plants and transgenic offspring plants.

In the November 1990 issue of *Bioworld*, in an article by Robbins-Roth *et al.* entitled "They Make it Happen in Biotech," Dr. Catherine Mackey, head of the DeKalb transformation research team, was picked as one of four scientists shaping the biotech industry's growth, Robbins-Roth *et al.*, Bioworld, p. 36 (Nov/Dec 1990). **(Exhibit J)**. The article refers to the achievement of genetically-engineered corn as "one of the Holy Grails" of agricultural biotechnology. The article then states that monocots such as corn "have been the toughest nuts to crack" in agricultural biotechnology. *Id.*

Similarly, *Agricultural Genetics Report* characterized the race for corn transformation as biotechnology's "run for the roses" and "Holy Grail":

> The Bottom Line: Well, more heard from in agricultural biotechology's run for the roses - corn transformation. As we have observed earlier in this space, stable transformation of maize has always been the Holy Grail of agricultural biotechnology.

Agricultural Genetics Report, March/April 1990, p. 2 **(Exhibit K)**.

The October 1990 issue of *Genetic Technology News* **(Exhibit L)** included a special section detailing the "breakthrough" represented by genetically engineered corn. The article states that "now we how for sure that it is possible to genetically engineer corn." Further, an article from *AG Biotechnology News* characterizes the development of this technology as "revolutionary." Freiberg, B., *AG Biotechnology News*, p. 26 (1990) **(Exhibit M)**.

The achievement of genetically engineered corn did not go unnoticed in the lay press either. *Investor'sDaily* characterized this achievement as "an advance that other scientists hailed yesterday as a breakthrough" **(Exhibit N)**. The *Rockford Register Star* characterized this achievement as "the launching point for a genetic engineering revolution." Steimel, D.,

Rockford Register Star, col. 1, (August 6, 1990) (**Exhibit O**). The *Chicago Tribune* quoted the Assistant director of the Washington University Center for Plant Science as the achievement being a "tremendous breakthrough." Gunset, G., *Chicago Tribune*. (April 19,1990) (**Exhibit P**). Moreover, the *Wall Street* Journal recognized the great achievement represented by the achievement of fertile, transgenic corn:

> While scientists have been able to get new genes into monocot plants, the plants previously have ended up sterile and unable to pass the new genes on in their seed.

Bishop, J. E., *The Wall Street Journal*, B1 (April 1990) (**Exhibit Q**).

Further evidence of the nonobviousness of the claimed invention is provided by the rapid acceptance by the art of the methodologies disclosed in the present application. Following the publication of the results achieved by the DEKALB research groups in July of 1990, research groups employing the transformation of callus by microprojectile bombardment accomplished the transformation of wheat, oats, barley, and sorghum. See Vasil *et al.*, U.S. Patent No. 5,405,765 (issued April 11, 1995); Y. Wan and P. G. Lemaux, *Plant Physiol.*, 104, 3 7 (1994); D.A. Somers *et al.*, *Bio/Technology* 10, 1589 (1992); A.M. Casas *et al.*, *PNAS USA*, 90, 11212 (1993) (**Exhibit R**).

This evidence demonstrates that, at best, it would have been "obvious to try" to those of ordinary skill in the art prior to the invention to arrive at the claimed subject matter. Tomes would not change this view because Tomes fails to disclose a single transgenic maize plant.

In view of the foregoing, Applicants respectfully request the removal of the rejection under 35 U.S.C. § 103.

F. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.